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A COMPREHENSIVE REVIEW ON THE ROLE OF CELL GROWTH AND APOPTOTIC GENES TOWARDS THE PROGRESSION OF CML

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ABSTRACT

The treatment of chronic myeloid leukemia (CML) has been revolutionized by the small molecule imatinib mesylate which is a kinase inhibitor. Imanitib was the first BCR-ABL targeted drug approved for the treatment of CML patients and it has significant response in most patients; however some patients are initially refractory to the drug or may develop resistance during the course of treatment. Impared drug binding have been identified as one of the major mechanisms of resistance for the drug is point mutation in kinase domain of BCR-ABL gene. Whereas the chronic phase of CML is dependent on BCR-ABL fusion gene, additional mutations are required for progression to BC. However, the significance of these mutations and the pathways they affect are poorly understood, hindered our ability to identify therapeutic targets and improve outcomes. According to some reports the incidence of Chronic Myeloid Leukemia (CML) is continuously increasing and expected to reach 100,000 patients every year by 2030. Though the discovery of Imatinib Mesylate (IM) has brought a revolutionary change in CML treatment, 20% patients show resistance to this tyrosine kinase inhibiter (TKI). Therefore, it is important to identify markers, which can help to investigate the occurrence and prognosis of CML. In this review, we will summarize the role of the cell growth and apoptotic genes in progression of chronic phase of CML to accelerated phase and correlation between these genes and susceptibility of person towards the CML.

KEYWORDS: Chronic myeloid leukemia, CML, BCR-ABL, Tyrosine kinase inhibitor, TKI, kinase domain, KD, Chronic phase CP, Blast chrisis, BC.

INTRODUCTION

Cancers can be caused by changes in DNA (mutations) that turn on oncogenes or turn off tumor suppressor genes. Over the past decade, scientists have made great improvement to understand how certain changes in DNA can cause normal bone marrow cells to become leukemia cells.

Chronic myeloid leukemia (CML) is one of the most common leukemia. CML is described by a balanced genetic translocation, t(9;22)(q34;q11.2), in which the Abelson gene (*ABL1*) from chromosome 9q34 fused with the breakpoint cluster region (BCR) gene on chromosome 22q11.2. This genetic translocation is known as the Philadelphia chromosome. The molecular consequence of this translocation is the generation of a *BCR-ABL1* fusion oncogene, which in turn translates into a *BCR-ABL1* oncoprotein , which is the type of protein called a tyrosine kinase. This protein causes CML cells to grow and divide out of control. In a very small number of CML cases, the leukemia cells have the *BCR-ABL* oncogene but not the Philadelphia chromosome. It's thought that the *BCR-ABL* gene must form in a different way in these people. In an even smaller number of people who seem to have CML, neither the Philadelphia chromosome nor the *BCR-ABL* oncogene can be found. They might have other, unknown oncogenes causing their disease and are not considered to truly have CML.

Imatinib is a tyrosin kinase inhibitor, which has proven to be very effective in achieving high remission rates and improving prediction of treatment outcome. However a fraction of CML patients presents with resistance to this drug. Imatinib-based therapies were discontinued due to resistance and intolerance/noncompliance. the resistance for imatinib is developed due to the occurrence of point mutations in the BCR-ABL KD(kinase domain), although BCR-ABL amplification and impaired signaling pathways may contribute to the resistance. Other possible BCR-ABL independent mechanisms that influence resistance include reduced bioavailability of imatinib within Ph-positive cells, cytogenetic changes, disfunctionality of p53, and activation of alternative signaling pathways that promote cell survival and proliferation and reduced apoptosis. The achievement of

targeted therapy in CML has not yet been imitated in other malignancies since cancer is most frequently the result of stepwise accumulation of multiple genetic defects.

How can only one mutation that is BCR-ABL1 is sufficient for disease initiation and maintenance? And is it really only BCR_ABL mutation that causes CML? Physiologic BCR-ABL1 fusion gene may be inadequate for development of a CML-like disease. Treatment of such types of diseases requires the fast and accurate identification of genetic deformities predictive of therapeutic response knowledge of the genetic alterations in cancer can help determine a treatment plan. Some treatments particularly, some targeted therapies are effective only for people whose cancer cells have specific genetic alterations that cause the cells to grow out of control. . Studying the frequencies and pattern of CML-related gene mutations across different diagnostic subcategories is important because it can make easy selection of targeted therapies, help us understand possible pathways or resistance mechanism, and serve as a scaffold to discover applicable clinical associations as our mutation database is populated in order to provide more improved predictive and prognostic information on our patients to guide treatment and to make right clinical decision.

Literature Review- CML characterized with the genetic abnormality in their blood cells called Philadelphia (Ph) chromosome.

The chromosomal translocation (t 9:22) (q 34:q11) causes BCR-ABL fusion gene. This rearrangement is known as the Philadelphia chromosome. The Ph chromosome causes the production of an enzyme called tyrosin kinase (1).The normal ABL gene performs several functions .ABL gene encodes tyrosine kinase. ABL is activated to stimulate cell proliferation and differentiation(2,3). BCR- ABL causes malignancy by three major mechanisms namely decreased adhesion to stroma cells and extracellular matrix . Constitutively active cell proliferation(4). And failed apoptosis control(5). Malignant transformation by BCR-ABL is critically dependent on its tyrosin kinase activity. As a result multiple signalling pathways are activated. Inhibition of such activity could be the most logical means to prevents tyrosin kinase from exerting its role in the oncogenic pathway. Several tyrosin kinase inhibitors have been discovered.(6).Cml is one of the most common adult leukemia originl data of cml incidence was 0.8 to 2.2 per 100,000 population(7).However most of the data from population report chronic and acute form of leukemia as a single entity , these data may not represent the true occurrence(8).Some studies reported that Asian countries have lower incidence of CML measured with the US. This variation may not apply to all countries(9).There are also reports of higher frequencies of CML in leukemias 40% to 80% compared with 25% in the US. Indian patients with CML are from younger age group(35 to 40 years) compared with western countries where age group of CML patient relies between 50 to 60 years. Hospital based data also suggested that there may be younger age group represents the cml cases in India(10).According to current estimate every year 1 lack patients are diagnosed with CML which is a very serious health problem(11) .To control the disease incidence there is need of potential marker to detect the individuals prone to have CML. Development of imatinib mesylate(IM) which is a tyrosine kinase inhibitor has drastically improved patient survival and the prognosis of the disease. Major molecular response of drug in first 12 months is 22% after 24 months it increases to 44% and 81% after 10 years. Though imatinib is very effective to treat CML but some patients are not responding and acquired ressistance and intolerance. Approximately 20% of the patients show ressistance (12). Recent studies shows that the Mutations in kinase domain causes ressistance for drugs binding. kinase domain mutation is the main reason for the imatinib ressistance in the patients with CML (13). Some patients do not have kinase domain mutation but show increased level of BCR-ABL (14). Some patients do not expressed kinase domain mutation but show ressistance to imatinib treatment in BCR-ABL independent manner example- through the activation of SRC family kinases or adaptive granulocyte –macrophage colony stimulating factor secretion(15,16).BCR-ABL1 mutation is the most studied mechanism of TKI ressistance in CML.Patients with ressistance to tyrosin kinase inhibitor but do not have mutation in BCR-ABL kinase domain may have another kind of mutations . the other studies also suggest that the other mechanisms of imatinib ressistance are known to exist (17) .Ras is a monomeric GTPases involved in cell signalling pathways responsible for cell growth and differentiation . Mutation in Ras in GTP bound form can causes cancers in humans (18).Prevelance of mutation in K-RAS and N-RAS genes has also been found in multiple myelomas(19). Mutations in the K-RAS and N- RAS also identified in AML(20) .

Some researchers detected IDH (Isocitrate dehydrogenate) mutations in the setting of both lymphoid and myeloid BC CML but not in CP CML patients.

On the other hand, in the same study it is confusing that the frequency of IDH gene mutations were found in BC CML (overall, 4/115 (3.5%) cases) is significantly lower than that noticed in blast phase MDS or MPN (22–25%).(21)

The main gene responsible for cell proliferation and survival in CP-CML patients is BCR-ABL fusion gene. Only few BCR-ABL independent genetic mutations are known in CML progression (22).

According to some reports the higher content of CpG methylated sites were observed in CML patients when compared with the control samples. It was also reported that the percentage of methylated CpG sites increases in BC-CML samples compared with CP-CML samples (23).

Some studies also showed that the identification of pathogenic somatic variants of epigenetic modifiers are common in CP-CML. Investigation of these kind of mutation can be used As a predictive biomarkers determining which is the best TKI for each individual (24).

Researchers investigate the mutations in IDH1 and IDH2 in acute myeloid leukemia (AML), chondrosarcoma, myelodysplastic syndromes, and cholangiocarcinoma (25-26). Mutant IDH (mutIDH), and its associated molecular pathways can be an attractive therapeutic targets for AML due to limited treatment option (27). But their prevalence and prognostic impact remain to be explored in large extensively characterized CML and AML.

Isocitrate dehydrogenase1(IDH1) and(IDH2) are homodimeric isoenzymes involved in cellular metabolism such as NADPH generation through the oxidative decarboxylation of isocitrate to a-ketoglutarate, epigenetic regulation, redox state and DNA repair .

IDH1 is found in the cytosol and in peroxisomes, while IDH2 is a mitochondrial enzyme. IDH1/2 mutations can cause the progression of various types of cancers . IDH3 forms heterotetrameric complexes in mitochondria, mutation in IDH3 are rarely seen in cancer, but some evidence shows that upregulation of wildtype IDH3 may contribute to various tumorigenic metabolic pathways (28). Due to limited methods of treatment of TKI resistant patients their is need to investigate other potential biomarkers to explored the predictive value of different biomarkers at the time of diagnosis including gene expression(29), protein expression(30), DNA methylation(31), miRNA expression(32) and SNP analysis(33).

The mechanism behind the apoptosis is evolutionarily preserved and is implemented by a family of proteins, called caspases. Caspases are cysteine proteases that are cleaved after an Asp residue in their substrates. They remains in the cell as inactive zymogenes and during stress condition activated by proteolytic cleavage; their activation is mainly controlled by the BCL2 family proteins (34).

BAX protein is a monomeric protein in the cytosol, which translocates into the mitochondria during apoptotic signaling and thereafter oligomerizes, that results into the release of apoptogenic factors like cytochrome c and the activation of the caspase cascade(35). It has also been found that high levels of BCR/ABL expression are responsible for the prevention of the early translocation of the pro-apoptotic proteins BAD and BAX from the cytosol to the mitochondrion after a apoptotic signal, this explains the resistance of cells that express high BCR/ABL levels to cytotoxic drugs (36).The bcr-abl1 fusion protein enhances cell survival and exerts antiapoptotic activity in CML cells, thus mediating resistance to apoptosis . Bcr-abl1 induces Bcl-XL, an antiapoptotic protein, through STAT5 phosphorylation (37). The bcr-abl1 fusion protein also blocks the cytochrome C release from mitochondria, activating anti-apoptotic pathway.

Single nucleotide polymorphisms (SNPs) may be related to CML progression (38) and to response to treatment (39,40). There is some evidence in the literature, reporting an association between various SNPs and the risk of development of CML. Some studies shows that BCL2 SNPs were associated with an increased risk of developing CML (41). Inhibition of apoptosis is, however, not considered to be the primary mechanism Bcr-Abl employs in CML progression. As seen with cells from CML patients, at early stages of the disease, Bcr-Abl level alone does not responsible to prevent drug-induced apoptosis draw attention that cellular context and disease stage is instrumental in Bcr-Abl-mediated effects(42). Caspase 8 gene encodes a member of the cysteine-aspartic acid protease (caspase) family mainly localizes in cytoplasm. Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis.

The higher expression of the anti-apoptotic molecules induced activation of STATs, which binds particularly to the regulatory elements of the DNA and regulate gene transcription. The permanent activation of the STAT pathway in neoplasia, including CML, leads to undesirable gene regulation and therefore modified processes such as apoptosis and cell proliferation (43).

CONCLUSION

Imatinib is a tyrosin kinase inhibitor which has been successfully introduced in CML therapy. However despite these successful attempts many patients developed ressistance against this drug. For such patients treatment options are limited. To discover new therapeutic agents researchers have been made number of attempts. The development of ressistance in some CML patients may be due to gene mutations in

some other genes such as growth and apoptotic genes. Thus molecular ressistance against imatinib may not only be caused by changes in BCR-ABL but also by other genes.There are only few studies reported related to genes other than BCR-ABL in CML patients. By studying these genes we can correlate mutations of these genes with the treatment outcome.

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